The International Journal of Lower Extremity Wounds

What is the best option for treating venous leg ulcer infection? Is it systemic or local Antimicrobials or a combination of both?   A retrospective Cohort Study

Journal:	*The International Journal of Lower Extremity Wounds*
Manuscript ID	IJLEW-2020-10-237.R2
Manuscript Type:	Original Paper
Keywords:	Chronic wounds < Lower Extremity Wound, Venous < Lower Extremity Wound, Wound infection < Diagnosis
Abstract:	Study aimed to find out best option (systemic or local antimicrobial or combination of both) for treating venous leg ulcer infection. Patients' files were reviewed retrospectively. Participants were divided into three groups. First group was treated by systemic antibiotics only (SABG). Second group received local antibiotics only (LABG). Third group was treated by combination of both (SLABG). Treatment strategies were compared based on multiple parameters using Pearson chi-squared test & relative risk (RR). 456 participants were identified: 153 patients in SABG, 152 in LABG and 151 in SLABG. It was found that SLABG group was statistically significantly better than other single treatment strategies regarding all parameters (except bacterial resistance): (i) ulcer healing within usual duration of 10-14 days was 2.4 time higher (RR 2.4, 95% CI: 1.84, 3.12), (ii) probability of not recurring ulcer was 2.6 time higher (RR 2.6, 95% CI: 1.98, 3.44), (iii) probability of not getting increased wound size or abscess or cellulites during therapy was 5 times higher (RR 5.3, 95% CI: 3.66, 7.74), (iv) probability of not developing septicemia was 40% higher (RR 1.4, 95% CI: 1.27, 1.64), (v) probability of not requiring surgical intervention was 30% higher (RR 1.3, 95% CI: 1.17, 1.47), (vi) fewer patients needed prolonged hospitalization and hence lower cost was 8 times more likely (RR 7.9, 95% CI: 5.01, 12.37), (vii) patients were at least 3 times more satisfied during treatment (RR 3.2, 95% CI: 2.44, 4.27). Probability of bacterial resistance was at least six times higher (RR 6.8, 95% CI: 3.16, 14.47) with SLABG and 5 times higher (RR 5.8, 95% CI: 2.7, 12.56) with SABG compared to LABG. Ultimately, combination of both systemic and local antimicrobials may be best option to treat venous leg ulcer infection with out- weight with emergence of antibiotic-resistance microorganism

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What is the best option for treating venous leg ulcer infection? Is it systemic or local Antimicrobials or a combination of both?   A retrospective Cohort Study

Abstract

Introduction:

Venous leg ulcer is a very common complain, for which patients usually seek medical help. This ulcer may arise due to incompetent venous valves with subsequent venous stasis and hypertension. Many of these ulcers or wounds are infected by micro-organisms and show signs and symptoms of clinical infection. The existence of such infection may delay the healing of the ulcer. Three main ways are used to prevent and manage clinical infection in venous leg ulcers: systemic antibiotics, topical antibiotics and the combination of both. This study aims to find out the best option (systemic or local antimicrobial or combination of both) for treating venous leg ulcer infection.

Method:

A retrospective cohort study reviewed files of patients who had been treated for venous leg ulcer infection. Participants were divided into three groups. First group was treated by systemic antibiotics only (SABG). Second group received local antibiotics and or antiseptics only (LABG). Third group was treated by combination of both strategies (SLABG). Treatment strategies were compared based on multiple parameters using Pearson chi-squared test and relative risk (RR).

Results: 456 participants were identified: 153 patients in SABG, 152 in LABG and 151 in SLABG. It was found that the SLABG group was statistically significantly better than the other single treatment strategies in terms of all the parameters (except bacterial resistance): (i) ulcer healing within the usual duration of 10-14 days was 2.4 time higher (RR 2.4, 95% CI: 1.84, 3.12), (ii) the probability of not recurring ulcer was 2.6 time higher (RR 2.6, 95% CI: 1.98, 3.44), (iii) the probability of not getting increased wound size or abscess or cellulites during therapy was 5 times higher (RR 5.3, 95% CI: 3.66, 7.74), (iv) the probability of not developing septicemia was 40% higher (RR 1.4, 95% CI: 1.27, 1.64), (v) the probability of not requiring surgical intervention was 30% higher (RR 1.3, 95% CI: 1.17, 1.47), (vi) the advantage of fewer patients needed prolonged hospital stay and hence lower cost was 8 times more likely (RR 7.9, 95% CI: 5.01, 12.37), (vii) the patients were at least 3 times more

satisfied during treatment (RR 3.2, 95% CI: 2.44, 4.27). The probability of bacterial resistance was at least six times higher (RR 6.8, 95% CI: 3.16, 14.47) under the combination modality (SLABG) and at least 5 times higher (RR 5.8, 95% CI: 2.7, 12.56) under the systemic modality (SABG) compared to local treatment strategy (LABG).

Conclusion: Combination therapy can achieve good results in terms of venous ulcer healing and infection control with reasonable duration, less complications, less recurrence rate and a good degree of patient satisfaction. The use of combination of both systemic and local antimicrobials may be the good option to treat venous leg ulcer infection with out- weight with the emergence of antibiotic-resistance micro-organism

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Introduction:

Venous leg ulcer is a type of chronic and complicated wound that might occur due to venous insufficiency. Venous leg ulcer may last for weeks or months or years or never heals. There are many factors which can affect ulcer healing such as age of the patient, size and duration of the ulcer and other risk factors which might further delay wound or ulcer healing. In addition, it has been reported that this problem (venous leg ulcer) is more common in women than in men. 1, 2

The incidence of venous leg ulcer is different from one area to another. The incidence of this disease in Australia and Europe is 0.1% to 0.3% .3 Meanwhile, in UK the prevalence of venous leg ulceration is 0.023% in London, 0.044% in Hull and East Yorkshire and 0.039% in Bradford and Airedale. The lower percentage in the UK surveys versus other parts of the world may be due to the differences in management of the disease or definition of the condition or both. 4, 5

Venous leg ulcer might present with specific clinical features. The patient may complain from mild to moderate or severe leg pain which might get better by leg elevation. Venous leg ulcer characterized by irregular, slopping edges and the localized surrounding skin is hard and with pigmentation due to death of erythrocytes, scar tissue formation and localized edema. In addition, there are superficial dilated veins (varicosities) nearby the ulcer or might be distributed to involve the whole leg. 6

The diagnosis of venous leg ulcer depends upon clinical history, physical examination and investigations. These investigations or tests might include assessment of the leg veins using doppler U/S or venous duplex scan. Ankle-Brachial Pressure Index (ABPI) greater than 0.8 can exclude the co-existence of peripheral arterial disease which can influence the treatment of venous ulcer. 7

The quality of life can be disturbed greatly in the patients with leg ulcers. Many problems have been reported such as reduction of work ability, leisure activities, sleep disturbance, feeling of un-well, reduced or sometimes impaired motility, social isolation and others. 8

Leg ulcer is a very costly to the patients and to the health institutions. The cost of treatment of this condition (unhealed leg ulcer) in UK in 2001 was around 130,000 GBP annually. In Germany the total mean annual cost for this disease has been estimated around 9060 EUR per patient according to 2006 price. 9

Venous leg ulcer can be infected easily because moist and chronic ulcer is an ideal medium for bacterial colonization. It has been reported that about 80% to 100% of these infected ulcers might be caused by bacterial infection. There are many types of micro-organism which can be responsible for such infection, but the most common

types are *Staphylococcus aureus* and *Pseudomonas aeruginosa.* This infection can further complicate the problem and delay healing of ulcer. 10, 11 The load or the density of infective agents, the diversity of micro-organism at the same episode of infection, specific strains (such as Staphylococcus *aureus, Pseudomonas aeruginosa and heamolytic streptococci)* and others can affect and further complicate wound infection. 12, 13

The classical clinical picture of infection includes pain, tenderness, hotness, redness, swelling and discharge. However, it has been found that these features may not always present in venous leg ulcer infection. Sometimes patient might have delayed wound healing, unexpected pain, bad smell, dark discoloration, devitalized tissue (necrotic and sloughy). Whatever the presentation (classical or not), the anti-microbial therapy should be started. 14,15

The two main modalities, which are used to treat venous leg ulcer infection, are systemic route (systemic antibiotics) and local route (local antibiotic). 15 Antibiotics (systemic or local) are substances which destroy or inhibit the growth of micro-organisms. There are many types of systemic antibiotics such as Penicillin group (Amoxicillin), Cephalosporin group (cephalexin), Aminoglycosides (gentamicin), Macrolides (erythromycin) and others. 14,15

The topical or local anti-microbial agents include topical antibiotics and antiseptic. Antiseptics are mainly lotions with antimicrobial properties which are used to irrigate or to cleanse the wound. They are usually designed to have short contact time with the wound surface unless they are used as packs or soaks. These antiseptics include products based in chlorhexidine, povidone-iodine, hydrogen peroxide, cadexomer iodine, silver-based, honey-based, potassium permanganate and others. 15 On the other hand, the topical antibiotics are designed to have longer contact time with wound surface area which is typically until the next dressing change. These topical antibiotics are mainly cream, or ointment such as fusidic acid, mupirocin, neomycin sulphate, gentamycin and others. 14,15

In the clinical practice different plans are used for management of venous leg ulcer infection. Some use systemic antibiotics only, other use local antimicrobial only (local antibiotics and or antiseptics) and others uses the combination of both. Therefore, **the aim of this current study** is to find out which option is the optimum choice to achieve the best results regarding wound (ulcer) healing and other related aspects. In other words, this study aims to compare between these three different options (systemic antibiotics only, local antimicrobial only or the combination of both) with regards to infection control.

Method

This is a retrospective cohort study which reviewed files and notes of patients who had medical treatment for venous leg ulcer infection. The study was conducted at our institution (Kerbala medical university / Imam Hussein medical city hospital/ Kerbala/Iraq). Consent was taken from the patients to do this research. The study has been reported in line with the STROCSS criteria. 16

Files and notes of the patients with venous leg ulcer infection who were already admitted, treated and then discharged from the surgical ward were reviewed retrospectively. Venous leg ulcer infection was defined by depending on clinical history and physical examination such as the presence of pain, tenderness, hotness, redness, and discharge and then confirmed later on by culture and sensitivity. Apart from age, race and gender, these patients were chosen and included precisely with very accurate inclusion criteria. These inclusion criteria were: (i) patients with venous type ulcer only and the size (the diameter) of the wound(ulcer) ranged from 2-3cm (ii) patients should be admitted for the first time only(iii) anti-microbial therapy should be started within 1st 48 hour after admission with venous leg ulcer infection as empirical treatment and then change according to C/S results(iv) the diagnosis of venous ulcer must be confirmed by clinical assessment and by confirmatory tests (v) no known history of specific antibiotic resistance. (vi) The sensitivity of micro-organism to the antibiotic should be confirmed by C/S test before the start of therapy whether local or systemic. (vii) Venous leg ulcer infection should be caused by single pathogen only. (viii)In addition to treatment of venous ulcer infection, the venous ulcer itself and other varicosities should be treated as well in the form of leg elevation or compression stockings, or medications (Pentoxifylline) or any other form. (IX) The duration of antibiotic use should be 10-14 days (as a maximum) for all participants.

All the included participants were seen in A&E (accident and emergency) department or in out-patient clinics with proper and full clinical assessment. The duration of illness before seeking medical advice was nearly the same for all participants. Then they had routine blood tests, ulcer swab for culture and sensitivity, ABPI, venous duplex scan, urine analysis, imaging and other investigations. After that, they had been admitted to the surgical wards with close monitoring. All of them received same type, dose and duration of subcutaneous VTE prophylaxis.

The study included only the participants who had daily wound care and change of dressing during the period of admission. In addition, all of them remained in the hospital until complete healing of the venous leg ulcer infection. The entire participants were selected to have nearly the same level of physiological and

pathological derangement before admission in terms of vital signs (pulse rate, blood pressure, respiratory rate, temperature,O2 saturation), degree of clinical infection and density and duration of infection in order to avoid any bias in the study. In other words, all the included patients should have nearly the same degree or level of infection in terms of clinical picture and density of infection according to clinical assessment and laboratory confirmation. All the participants received the treatment within first 48 hour of admission. They started on the same empiric antibiotic protocol and then changed according to the result of C/S

On the other hand, the patients which were excluded from the study were (exclusion criteria): (I) arterial leg ulcer or diabetic foot or malignant ulcer or other types of ulcers or big size ulcer (ii) immune-compromised patients such as patients with DM, AIDS, steroid therapy or any other condition which might suppress the immunity. (iii)Patients who had previous admission for venous leg ulcer (IV) patients who had resistance to specific antibiotic (v) patients with renal or hepatic impairment (vi) patients who had sever degree of infection in terms of clinical picture, density of infection or the presences of multiple strains at the same episode of infection (vii) patients who had infection caused by more than single pathogen (viii)penicillin allergy.

Files and notes of the patients with the inclusion criteria were reviewed retrospectively and data was collected on participants' profile in terms of multiple variables. These variables were age, gender, BMI (less than 18 underweight, 18-25 normal BMI, 25-30 overweight, above 30 obese),side of ulcer (left or right), the type of micro-organism, type of antibiotic used, presence of co-morbidities such as (hypertension, ischemic heart diseases , cerbro-vascular accidents or others), socio-economic state (live alone or with family), smoking and alcohol consumption.

The retrospective review of the included patients' notes documented the mode of therapy whether it was systemic antibiotics only; local antimicrobial (local antibiotics and or antiseptics)only or the combination of both(the difference between local anti-biotic and local antiseptics and the definitions of both is already explained in the introduction). As a result, the study divided the included participants into three groups. First group was on systemic antibiotics only whether oral or intravenous or intramuscular or any other systemic route (SABG). The second group received local antibiotics (local antibiotics and or antiseptics) only (LABG). And the third group was treated by both strategies: combination of both systemic and local antimicrobial agents (SLABG).

As mentioned above: this is a retrospective study and, therefore, the decision of the use of the mode of therapy (whether systemic or local antibiotics or both) is totally related to the original treating physician. However, in order to avoid any bias, the

entire participants were selected to have nearly the same level of physiological and pathological derangement and degree of ulcer infection.

Then a comparison was done between these three groups in terms of the following parameters: (i) duration needed to achieve complete ulcer healing. Duration of more than 10-14 days was regarded as long duration (ii) recurrence of ulcer. In other words, if venous leg ulcer infection re-occur within less than 6 months after initial discharge with complete healing, this can be considered as a bad treatment strategy (iii) development of bacterial resistance during the course of therapy or later on. And this should be confirmed by C/S test (IV) increase in wound (ulcer) size and or local spread of infection to form cellulites or abscess. During admission wound or ulcer must be checked frequently to see if there is increase or decrease of its size during the course of treatment. In addition, the development of complications such as cellulites and or abscess must be noticed (v) systemic spread of infection: septicemia. This should be confirmed by clinical picture and blood culture. (VI) the need for surgical intervention: abscess drainage, graft, flap, wound excision, leg amputation, etc (vii) Length of Hospital Stay (LOS). Hospital admission of 10-14 day was regarded as normal (viii) Cost: a cost of 20 dollar per day and 250 dollar per 10-14 day of admission was regarded as ordinary by the study (ix) patient satisfaction and quality of life during the period of treatment in terms of decreased pain, reduced odor, reduced exudates and other prodormal symptoms (x) drug side effects during or after the course of therapy such as allergic reaction or skin rash or renal toxicity or interaction with other drugs or any other significant side effect.

Data was collected on Microsoft® Excel version 16. Statistical analysis was done using the chi-squared test to compare the SLABG, SABG and LABG patients using statistical software package SPSS version 26 and relative risk was calculated using the software package MEDCALC.

Results

456 participants treated between 2015-2018 were enrolled in the study. Their ages ranged from 35 to 89 year. 58% (262/456) of these patients were female. 330 (72%) were overweight, 61 (13%) were obese and the others had normal BMI. 56% (254/456) patients had left sided venous leg ulcer. 195 (43%) patients had their infection caused by Staphylococcus *aureus* for which systemic flucloxacillin and local fucidic acid were used. 145 (32%) patients had got ulcer infected with *Pseudomonas aeruginosa* for which systemic ceftriaxone and local gentamicin were used.And the others 25% infected by *streptococcus pyogens* for which systemic penicillin and local erythromycin were used.309 (68%) had co-morbidities such as hypertension (HTN),

ischemic heart diseases (IHD) , cerbro-vascular accidents (CVA), transient ischemic attack (TIA), peripheral vascular diseases (PVD) or others. 94% (429/456) live with their families, while the rest 6% live in residential home and none of them lives alone. 72% (330/456) was smoker and 4% (18/456) was alcohol consumers. See table 1 below.

Table 1: Participants profile

Patient Characteristics	Total (n=456)	SLABG (n=151)	SABG (n=153)	LABG (n=152)	P-value
	Number (%)	Number (%)	Number (%)	Number (%)	
Age in years: mean (SD)	59.14 (16.5)	56.48 (16.8)	63.43 (15.3)	57.45 (16.6)	<.001
Gender					.99
Male	194 (42.5)	64 (42.4)	65 (42.5)	65 (42.8)	
Female	262 (57.5)	87 (57.6)	88 (57.5)	87 (57.2)	
BMI					
Normal	65 (14.3)	21 (13.9)	22 (14.4)	22 (14.5)	1.0
Overweight	330 (72.4)	110 (72.8)	110 (71.9)	110 (72.4)	
Obese	61 (13.4)	20 (13.2)	21 (13.7)	20 (13.2)	
Side of venor ulcer					.99
Left	254 (55.7)	84 (55.6)	85 (55.6)	85 (55.9)	
Right	202 (44.3)	67 (44.4)	68 (44.4)	67 (44.1)	
Type of pathogen					1.0
Staphylococcus aureus	195 (42.8)	65 (43.0)	65 (42.5)	65 (42.8)	
Pseudomonas aeruginosa	145 (31.8)	48 (31.8)	49 (32.0)	48 (31.6)	
Streptococus Pyogense	116 (25.4)	38 (25.2)	39 (25.5)	39 (25.7)	
Antibiotics					1.0
F&F	195 (42.8)	Both 65 (43.0)	Flu-clox 65 (42.5)	fucidic acid 65 (42.8)	
C&G	145 (31.8)	Both 48 (31.8)	ceftriaxone 49 (32.0)	Gentamicin 48 (31.6)	
P&E	116 (25.4	Both 38 (25.2)	Penicillin 39 (25.5)	erythromycin 39 (25.7)	
Co-morbidities					1.0
IHD	72 (15.8)	24 (15.9)	24 (15.7)	24 (15.8)	
CVA	63 (13.8)	21 (13.9)	21 (13.7)	21 (13.8)	
TIA	66 (14.5)	22 (14.6)	22 (14.4)	22 (14.5)	
PVD	39 (08.6)	12 (07.9)	14 (09.2)	13 (08.6)	
HTN	69 (15.1)	23 (15.2)	23 (15.0)	23 (15.1)	

No co-morbidities	147 (32.2)	49 (32.5)	49 (32.0)	49 (32.2)	
Living status					.56
With family	429 (94.1)	140 (92.7)	146 (95.4)	143 (94.1)	
In residential home	27 (5.9)	11 (7.3)	7 (4.6)	9 (5.9)	
Smoking					.98
Smokers	330 (72.4)	110 (72.8)	110 (71.9)	110 (72.4)	
Non-smokers	126 (27.6)	41 (27.2)	43 (28.1)	42 (27.6)	
Alcohol consumption					1.0
Drinkers	18 (3.9)	6 (4.0)	6 (3.9)	6 (3.9)	
Non-Drinkers	438 (96.1)	145 (96.0)	147 (96.1)	146 (96.1)	

Chi-squared test or ANOVA (as appropriate) was used to compare the SLABG, SABG and LABG patients.

Comparison of treatment strategies SABG, LABG and SLABG in terms of (i) the duration needed to achieve ulcer healing (ii) ulcer recurrence:

Table 2 shows that most patients 71% (107/151) who had received both systemic and local antimicrobial therapy (SLABG) had achieved complete ulcer healing and infection control within the standard period (10-14 day). On the other hand, only around 30% of the patients (48/153) who received systemic antibiotics only (SABG) and those who had local antibiotics only (LABG: 45/152) got ulcer healed within 10-14 days. Ulcer healing within the usual duration of 10-14 days was 2.4 time higher (relative risk 2.4, 95% CI: 1.84, 3.12) under the combination modality (SLABG) compared to other single treatment strategies.

Similarly, the study revealed that most of patients (72%) who were treated by a combination modality (SLABG) had not got ulcer recurrence within six months after initial discharge (109 out of 151). On the other hand, fewer patients (around 30%) in the other groups (44/153 in SABG and 42/152 in LABG) did not get recurrences of the ulcer within 6 months after initial healing, see table 2. The chi-squared test confirmed that the significant association between treatment strategies and recurrence rate of ulcer ($P<.001$). The probability of not recurring ulcer was 2.6 time higher (relative risk 2.6, 95% CI: 1.98, 3.44) under the combination modality (SLABG) compared to other single treatment strategies. See table 2 below:

Table 2: Duration needed to achieve ulcer healing, ulcer recurrence, development of bacterial resistance, increase in wound size and or abscess or cellulites during therapy, and development of septicemia and the need for surgical intervention according to treatment strategies

Parameters	SLABG: 151 No. (%)	SABG: 153 No. (%)	LABG: 152 No. (%)	P-value	RR(SL vs L) (95% CI)

				<.001	
Duration of ulcer healing				<.001	
Within 10-14 day	107 (71)	48 (31)	45 (30)		2.4
More than 14 day	44 (29)	105 (69)	107 (70)		(1.84, 3.12)
Ulcer recurrence within 6 months				<.001	
No	109 (72)	44 (29)	42 (28)		2.6
yes	42 (28)	109 (71)	110 (72)		(1.98, 3.44)
Bacterial resistance				<.001	
No	104 (69)	112 (73)	145 (95)		0.72
yes	47 (31)	41 (27)	7 (5)		(0.65, 0.81)
Abscess or cellulites				<.001	
No	127 (84)	25 (16)	24 (16)		5.3
yes	24 (16)	128 (84)	128 (84)		(3.66, 7.74)
Septicemia				<.001	
No	142 (94)	114 (75)	98 (65)		1.4
Yes	9 (6)	39 (25)	54 (35)		(1.27, 1.64)
Surgical intervention				<.001	
No	138 (91)	110 (72)	106 (70)		1.3
Yes	13 (9)	43 (28)	46 (30)		(1.17, 1.47)

P-value is calculated based on Chi-squared test to compare the SLABG, SABG and LABG patients. SL: SLABG, L: LABG. RR: Relative Risk, Bold indicates the outcome category for the RR.

Comparison of treatment strategies in terms of (iii) development of bacterial resistance (IV) increase in wound (ulcer) size and or local spread of infection to form cellulites or abscess:

It had been found, see table 2, that 31% of the patients (47/151) who had received both systemic and local antimicrobial therapy (SLABG) had developed bacterial resistance. Nearly a similar number of the patients 27% (41/153) who received systemic antibiotics only (SABG) had got the same problem (emergence of antibiotics-resistant micro-organism). Meanwhile, only 5% patients who had local antibiotics and or antiseptics (LABG: 7/152) had got bacterial resistance. Therefore, the probability of no bacterial resistance was 28% lower (relative risk 0.72, 95% CI: 0.65, 0.81) under the combination modality (SLABG) compared to local treatment strategy (LABG). Treatment strategy SABG also had the similar lower probability.

On the contrary, most of patients (127/151=84%) who were treated by a combination modality (SLABG) had not got increased wound size or abscess or cellulites during therapy. On the other hand, only very few patients (16%) in the other groups (25/153 in SABG and 24/152 in LABG) had not got increased wound size or abscess or cellulites during therapy. Chi-squared test confirmed the significant

association between treatment strategies and wound size (*P*<.001). The probability of not getting increased wound size or abscess or cellulites during therapy was more than 5 time higher under combination therapy (SLABG) compared to single treatment strategies (relative risk 5.3, 95% CI: 3.66, 7.74).

Comparison of treatment strategies in terms of (v) systemic spread of infection: septicemia (VI) the need for surgical intervention: abscess drainage, graft, flap, wound excision, leg amputation, etc:

The study revealed that very few patients (9 out of 151: 6%) in the SLABG group (the patients who had received both systemic and local antimicrobial therapy) had developed septicemia. Whereas, this percentage was much higher (at least 25%) in the other groups. 25% (39/153) who received systemic antibiotics only (SABG), and 35% (55/152) who had local antibiotics only (LABG). Similarly, only 9% of patients who were treated by a combination modality (SLABG 13/151) had required surgical intervention in the form of abscess drainage or skin graft or flap while around 30% patients in the other groups (43/153 in SABG and 46/152 in LABG) needed surgical intervention in the form of abscess drainage or skin graft or flap See table 2 for details. The probability of not developing septicemia was 40% higher under combination therapy (SLABG) compared to single treatment strategy of LABG (relative risk 1.4, 95% CI: 1.27, 1.64). Similarly, the probability of not requiring surgical intervention was 30% higher under combination therapy (SLABG) compared to single treatment strategy of LABG (relative risk 1.3, 95% CI: 1.17, 1.47).

Economic evaluation: Comparison of treatment strategies in terms of (vii) length of hospital stay (LOS) and (viii) Cost:

Table 3 presents the comparative results for length of hospital stay and related costs and patient satisfaction. It had been found that 87% (133/153) patients, who were treated by systemic antibiotics only (SABG), and 89% (135/152) patients, who received local antibiotics and or antiseptics only (LABG), had prolong hospital stay (more than 14 day) with subsequent more cost (more than 250 dollar). Meanwhile, only 12% patients (18/151) who had treated by the combination of both systemic and local antimicrobial agents (SLABG) had prolong admission and more cost. This advantage of fewer patients needed prolonged hospital stay and hence lower cost of treatment under SLABG treatment strategy over the other two strategies was statistically significant (P<.001) and 8 times more likely (relative risk 7.9, 95% CI: 5.01, 12.37).

Table 3: Length of hospital stay (LOS), Cost and patient satisfaction according to treatment strategy

Parameters	SLABG: 151	SABG: 153	LABG: 152	P-	RR ($_{SL\,vs\,L}$)

	No (%)	No. (%)	No. (%)	value	(95% CI)
Length of stay				<.001	
Usual: 10-14 days	133 (88)	20 (13)	17 (11)		7.9
Prolong: > 14 days	18 (12)	133 (87)	135 (89)		(5.01, 12.37)
Cost				<.001	
Usual: 250 dollar	133 (88)	20 (13)	17 (11)		7.9
Costly: >250 dollar	18 (12)	133 (87)	135 (89)		(5.01, 12.37)
Patient satisfaction				<.001	
Satisfied	125 (83)	47 (31)	39 (26)		3.2
Not satisfied	26 (17)	106 (69)	113 (74)		(2.44, 4.27)

P-value is calculated based on Chi-squared test to compare the SLABG, SABG and LABG patients. SL: SLABG, L: LABG. RR: Relative Risk, Bold indicates the outcome category for the RR.

Comparison of treatment strategies in terms of (ix) patient satisfaction and quality of life during the period of treatment: pain and other prodormal symptoms (x) drug side effects:

Table 3 shows that 83% (125/151) of the patients who had received combination treatment (SLABG) were satisfied during the course of treatment in terms of decreased pain, reduced odor, reduced exudates and other prodormal or constitutional symptoms. On the other hand, most of the patients, around 70% of patients who did not have combination treatment (106/153 in SABG and 113/152 in LABG) were not satisfied during the therapy. They were upset, unwell and with pain and other prodormal symptoms. The patients who had received combination treatment (SLABG) were at least 3 times more satisfied during the course of treatment compared to single treatment strategies (relative risk 3.2, 95% CI: 2.44, 4.27).

Regarding the development of drug side effects: apart from emergence of resistant micro-organism, none of the patients in all three groups had got significant side effects

Discussion and Conclusion

Venous leg ulcer is defined as chronic and complicated wound that usually affects medial side of the leg. The real underlying pathology is not well known. However, there are some mechanisms which might explain such ulcer. It is thought that this venous ulceration might arise due to incompetent venous valvular system. This in turn can lead to venous stagnation and then extravasations of blood and mediators of inflammation underneath the skin with subsequent tissue breakdown and ulcer formation. 17

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In addition, this venous ulcer almost always can get infected with multiple pathogens. And this infection can further delay ulcer healing and can cause many problems to the patients. Therefore, the key point is to control such infection in order to ensure safe healing of the venous ulcer. 18

To deal with venous ulcer, two important points should be taken into consideration. First point is the management of incompetent valves and other dilated veins or varicosities. The second point is infection control which is the most important and vital step in the whole process.18,19 Many ways are usually followed to treat venous leg ulcer infection such as systemic antibiotics or local antibiotics or local antiseptics or a combination of systemic and local routes. For each option there are some advantages and drawbacks. This current study aimed to shine the light and to find out which option is the best in terms of achievement of safe ulcer healing and patient satisfaction. The significance of this current study is great because it can improve health practice with subsequent achievement of patient safety. 19, 20

This current study revealed that best results can be achieved by combination of systemic antibiotics and local antibiotics. It had been found most of the participants, who had both systemic and local antimicrobials showed these results: (i) they had achieved infection control and ulcer healing within reasonable duration(10-14 days) (ii) they had not got recurrence of ulcer within 6 months after initial healing (iii) they had not got complications such as cellulitis or abscess or septicemia during or after the course of therapy (iv) they did not required surgical intervention in the form of abscess drainage or skin graft or flap or leg amputation during treatment period (v) they had not stayed in the hospital for prolong period of admission and without extra cost (vi) they were satisfied in terms of decreased pain, reduced odor, reduced exudates and other prodormal or constitutional symptoms and (vii)they had not got significant drug side effects.

On the other hands, most of participants who had either systemic antibiotics only or local antibiotics only showed the following results: (i) they had not achieved infection control and ulcer healing within reasonable duration(10-14 days) and they needed prolong duration to achieve wound healing. (ii) they had got recurrence of ulcer within 6 months after initial healing (iii) they had got complications such as cellulitis or abscess or increased wound size or septicemia during or after the course of therapy (iv) they required surgical intervention in the form of abscess drainage or skin graft or flap during treatment period (v) they had stayed in the hospital for prolong period of admission and with extra cost (vi) they were not satisfied in terms of decreased pain, reduced odor, reduced exudates and other prodormal or constitutional symptoms.

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Only a single drawback had been noticed with the use of systemic antibiotics. This is the emergence of antibiotics-resistant micro-organism. However, the advantages and patient satisfaction that could be achieved from systemic antibiotics can out-weight this single side effect.

Although there are similar studies in the same field, this current study is unique. Most of other studies compared between systemic antibiotics alone in one hand and between the use of local route alone in the other hand.21 Meanwhile, our study compared the combination of both routes in addition to the use of each route alone. Therefore, it is regarded as a new trial in the field of antimicrobial therapy for venous leg ulcer infection.

Meara et al which reviewed forty-five RCTs reporting 53 comparisons and recruiting a total of 4486 participants concluded that: at present, no evidence is available to support the routine use of systemic antibiotics in promoting healing of venous leg ulcers. However, the lack of reliable evidence means that it is not possible to recommend the discontinuation of any of the agents reviewed. 21

In terms of topical preparations, some evidence supports the use of cadexomer iodine. Current evidence does not support the routine use of honey- or silver-based products. Further good quality research is required before definitive conclusions can be drawn about the effectiveness of povidone-iodine, peroxide-based preparations, ethacridine lactate, chloramphenicol, framycetin, mupirocin, ethacridine or chlorhexidine in healing venous leg ulceration. In light of the increasing problem of bacterial resistance to antibiotics, current prescribing guidelines recommend that antibacterial preparations should be used only in cases of clinical infection, not for bacterial colonization. 21

As with other studies, this current research had some limitations. The retrospective mode of study can miss pitfalls related to the course of therapy, progression, prognosis and complications. Therefore, clinical trial with prospective stronger evidence is recommended for future studies. Although the sample size of this study was not calculated prospectively, the study had enough power as all the considered parameters were statistically significant. Moreover, this study was performed in a single center only and therefore a multi-center future study is highly recommended

Ultimately, our current study concluded that the combination of systemic antibiotics together with local antibiotics or antiseptics could achieve good results in terms of venous ulcer healing and infection control with reasonable duration, less complications, less recurrence rate and a good degree of patient satisfaction.

However, both groups SLABG and SABG had developed significantly higher bacterial resistance than the LABG group

Acknowledgement

We would like to acknowledge the participants and our institutions

Conflict of interest: None.

Source of Funding: None

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1. Minor comment number 1:   Please adjust the format of all references according to our current journal format. Our style is the Vancouver style without "issue number" in the reference list.
• Example No. 2-Gohel MS, Taylor M, Earnshaw JJ, Heather BP, Poskitt KR, Whyman MR. Risk factors for delayed healing and recurrence of chronic venous leg ulcers - an analysis of 1324 legs. Eur J of Vasc and Endovasc Surg 2005;29:747

My answer: Thank you very much. This was revised for all references as per your notice.

Manuscript –untracked

What is the best option for treating venous leg ulcer infection? Is it systemic or local Antimicrobials or a combination of both?   A retrospective Cohort Study

Abstract

Introduction:

Venous leg ulcer is a very common complain, for which patients usually seek medical help. This ulcer may arise due to incompetent venous valves with subsequent venous stasis and hypertension. Many of these ulcers or wounds are infected by micro-organisms and show signs and symptoms of clinical infection. The existence of such infection may delay the healing of the ulcer. Three main ways are used to prevent and manage clinical infection in venous leg ulcers: systemic antibiotics, topical antibiotics and the combination of both. This study aims to find out the best option (systemic or local antimicrobial or combination of both) for treating venous leg ulcer infection.

Method:

A retrospective cohort study reviewed files of patients who had been treated for venous leg ulcer infection. Participants were divided into three groups. First group was treated by systemic antibiotics only (SABG). Second group received local antibiotics and or antiseptics only (LABG). Third group was treated by combination of both strategies (SLABG). Treatment strategies were compared based on multiple parameters using Pearson chi-squared test and relative risk (RR).

Results:

456 participants were identified: 153 patients in SABG, 152 in LABG and 151 in SLABG. It was found that the SLABG group was statistically significantly better than the other single treatment strategies in terms of all the parameters (except bacterial resistance): (i) ulcer healing within the usual duration of 10-14 days was 2.4 time higher (RR 2.4, 95% CI: 1.84, 3.12), (ii) the probability of not recurring ulcer was 2.6 time higher (RR 2.6, 95% CI: 1.98, 3.44), (iii) the probability of not getting increased wound size or abscess or cellulites during therapy was 5 times higher (RR 5.3, 95% CI: 3.66, 7.74), (iv) the probability of not developing septicemia was 40% higher (RR 1.4, 95% CI: 1.27, 1.64), (v) the probability of not requiring surgical intervention was 30% higher (RR 1.3, 95% CI: 1.17, 1.47), (vi) the advantage of fewer patients needed prolonged hospital stay and hence lower cost was 8 times more likely (RR 7.9, 95% CI: 5.01, 12.37), (vii) the patients were at least 3 times more

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satisfied during treatment (RR 3.2, 95% CI: 2.44, 4.27). The probability of bacterial resistance was at least six times higher (RR 6.8, 95% CI: 3.16, 14.47) under the combination modality (SLABG) and at least 5 times higher (RR 5.8, 95% CI: 2.7, 12.56) under the systemic modality (SABG) compared to local treatment strategy (LABG).

Conclusion: Combination therapy can achieve good results in terms of venous ulcer healing and infection control with reasonable duration, less complications, less recurrence rate and a good degree of patient satisfaction. The use of combination of both systemic and local antimicrobials may be the good option to treat venous leg ulcer infection with out- weight with the emergence of antibiotic-resistance micro-organism

Introduction:

Venous leg ulcer is a type of chronic and complicated wound that might occur due to venous insufficiency. Venous leg ulcer may last for weeks or months or years or never heals. There are many factors which can affect ulcer healing such as age of the patient, size and duration of the ulcer and other risk factors which might further delay wound or ulcer healing. In addition, it has been reported that this problem (venous leg ulcer) is more common in women than in men. 1, 2

The incidence of venous leg ulcer is different from one area to another. The incidence of this disease in Australia and Europe is 0.1% to 0.3% .3 Meanwhile, in UK the prevalence of venous leg ulceration is 0.023% in London, 0.044% in Hull and East Yorkshire and 0.039% in Bradford and Airedale. The lower percentage in the UK surveys versus other parts of the world may be due to the differences in management of the disease or definition of the condition or both. 4, 5

Venous leg ulcer might present with specific clinical features. The patient may complain from mild to moderate or severe leg pain which might get better by leg elevation. Venous leg ulcer characterized by irregular, slopping edges and the localized surrounding skin is hard and with pigmentation due to death of erythrocytes, scar tissue formation and localized edema. In addition, there are superficial dilated veins (varicosities) nearby the ulcer or might be distributed to involve the whole leg. 6

The diagnosis of venous leg ulcer depends upon clinical history, physical examination and investigations. These investigations or tests might include assessment of the leg veins using doppler U/S or venous duplex scan. Ankle-Brachial Pressure Index (ABPI) greater than 0.8 can exclude the co-existence of peripheral arterial disease which can influence the treatment of venous ulcer. 7

The quality of life can be disturbed greatly in the patients with leg ulcers. Many problems have been reported such as reduction of work ability, leisure activities, sleep disturbance, feeling of un-well, reduced or sometimes impaired motility, social isolation and others. 8

Leg ulcer is a very costly to the patients and to the health institutions. The cost of treatment of this condition (unhealed leg ulcer) in UK in 2001 was around 130,000 GBP annually. In Germany the total mean annual cost for this disease has been estimated around 9060 EUR per patient according to 2006 price. 9

Venous leg ulcer can be infected easily because moist and chronic ulcer is an ideal medium for bacterial colonization. It has been reported that about 80% to 100% of these infected ulcers might be caused by bacterial infection. There are many types of micro-organism which can be responsible for such infection, but the most common

types are *Staphylococcus aureus* and *Pseudomonas aeruginosa.* This infection can further complicate the problem and delay healing of ulcer. 10, 11 The load or the density of infective agents, the diversity of micro-organism at the same episode of infection, specific strains (such as Staphylococcus *aureus, Pseudomonas aeruginosa and heamolytic streptococci)* and others can affect and further complicate wound infection. 12, 13

The classical clinical picture of infection includes pain, tenderness, hotness, redness, swelling and discharge. However, it has been found that these features may not always present in venous leg ulcer infection. Sometimes patient might have delayed wound healing, unexpected pain, bad smell, dark discoloration, devitalized tissue (necrotic and sloughy). Whatever the presentation (classical or not), the anti-microbial therapy should be started. 14,15

The two main modalities, which are used to treat venous leg ulcer infection, are systemic route (systemic antibiotics) and local route (local antibiotic). 15 Antibiotics (systemic or local) are substances which destroy or inhibit the growth of micro-organisms. There are many types of systemic antibiotics such as Penicillin group (Amoxicillin), Cephalosporin group (cephalexin), Aminoglycosides (gentamicin), Macrolides (erythromycin) and others. 14,15

The topical or local anti-microbial agents include topical antibiotics and antiseptic. Antiseptics are mainly lotions with antimicrobial properties which are used to irrigate or to cleanse the wound. They are usually designed to have short contact time with the wound surface unless they are used as packs or soaks. These antiseptics include products based in chlorhexidine, povidone-iodine, hydrogen peroxide, cadexomer iodine, silver-based, honey-based, potassium permanganate and others. 15 On the other hand, the topical antibiotics are designed to have longer contact time with wound surface area which is typically until the next dressing change. These topical antibiotics are mainly cream, or ointment such as fusidic acid, mupirocin, neomycin sulphate, gentamycin and others. 14,15

In the clinical practice different plans are used for management of venous leg ulcer infection. Some use systemic antibiotics only, other use local antimicrobial only (local antibiotics and or antiseptics) and others uses the combination of both. Therefore, **the aim of this current study** is to find out which option is the optimum choice to achieve the best results regarding wound (ulcer) healing and other related aspects. In other words, this study aims to compare between these three different options (systemic antibiotics only, local antimicrobial only or the combination of both) with regards to infection control.

Method

This is a retrospective cohort study which reviewed files and notes of patients who had medical treatment for venous leg ulcer infection. The study was conducted at our institution (Kerbala medical university / Imam Hussein medical city hospital/ Kerbala/Iraq). Consent was taken from the patients to do this research. The study has been reported in line with the STROCSS criteria. 16

Files and notes of the patients with venous leg ulcer infection who were already admitted, treated and then discharged from the surgical ward were reviewed retrospectively. Venous leg ulcer infection was defined by depending on clinical history and physical examination such as the presence of pain, tenderness, hotness, redness, and discharge and then confirmed later on by culture and sensitivity. Apart from age, race and gender, these patients were chosen and included precisely with very accurate inclusion criteria. These inclusion criteria were: (i) patients with venous type ulcer only and the size (the diameter) of the wound(ulcer) ranged from 2-3cm (ii) patients should be admitted for the first time only(iii) anti-microbial therapy should be started within 1st 48 hour after admission with venous leg ulcer infection as empirical treatment and then change according to C/S results(iv) the diagnosis of venous ulcer must be confirmed by clinical assessment and by confirmatory tests (v) no known history of specific antibiotic resistance. (vi) The sensitivity of micro-organism to the antibiotic should be confirmed by C/S test before the start of therapy whether local or systemic. (vii) Venous leg ulcer infection should be caused by single pathogen only. (viii)In addition to treatment of venous ulcer infection, the venous ulcer itself and other varicosities should be treated as well in the form of leg elevation or compression stockings, or medications (Pentoxifylline) or any other form. (IX) The duration of antibiotic use should be 10-14 days (as a maximum) for all participants.

All the included participants were seen in A&E (accident and emergency) department or in out-patient clinics with proper and full clinical assessment. The duration of illness before seeking medical advice was nearly the same for all participants. Then they had routine blood tests, ulcer swab for culture and sensitivity, ABPI, venous duplex scan, urine analysis, imaging and other investigations. After that, they had been admitted to the surgical wards with close monitoring. All of them received same type, dose and duration of subcutaneous VTE prophylaxis.

The study included only the participants who had daily wound care and change of dressing during the period of admission. In addition, all of them remained in the hospital until complete healing of the venous leg ulcer infection. The entire participants were selected to have nearly the same level of physiological and

pathological derangement before admission in terms of vital signs (pulse rate, blood pressure, respiratory rate, temperature,O2 saturation), degree of clinical infection and density and duration of infection in order to avoid any bias in the study. In other words, all the included patients should have nearly the same degree or level of infection in terms of clinical picture and density of infection according to clinical assessment and laboratory confirmation. All the participants received the treatment within first 48 hour of admission. They started on the same empiric antibiotic protocol and then changed according to the result of C/S

On the other hand, the patients which were excluded from the study were (exclusion criteria): (I) arterial leg ulcer or diabetic foot or malignant ulcer or other types of ulcers or big size ulcer (ii) immune-compromised patients such as patients with DM, AIDS, steroid therapy or any other condition which might suppress the immunity. (iii)Patients who had previous admission for venous leg ulcer (IV) patients who had resistance to specific antibiotic (v) patients with renal or hepatic impairment (vi) patients who had sever degree of infection in terms of clinical picture, density of infection or the presences of multiple strains at the same episode of infection (vii) patients who had infection caused by more than single pathogen (viii)penicillin allergy.

Files and notes of the patients with the inclusion criteria were reviewed retrospectively and data was collected on participants' profile in terms of multiple variables. These variables were age, gender, BMI (less than 18 underweight, 18-25 normal BMI, 25-30 overweight, above 30 obese),side of ulcer (left or right), the type of micro-organism, type of antibiotic used, presence of co-morbidities such as (hypertension, ischemic heart diseases , cerbro-vascular accidents or others), socio-economic state (live alone or with family), smoking and alcohol consumption.

The retrospective review of the included patients' notes documented the mode of therapy whether it was systemic antibiotics only; local antimicrobial (local antibiotics and or antiseptics)only or the combination of both(the difference between local anti-biotic and local antiseptics and the definitions of both is already explained in the introduction). As a result, the study divided the included participants into three groups. First group was on systemic antibiotics only whether oral or intravenous or intramuscular or any other systemic route (SABG). The second group received local antibiotics (local antibiotics and or antiseptics) only (LABG). And the third group was treated by both strategies: combination of both systemic and local antimicrobial agents (SLABG).

As mentioned above: this is a retrospective study and, therefore, the decision of the use of the mode of therapy (whether systemic or local antibiotics or both) is totally related to the original treating physician. However, in order to avoid any bias, the

entire participants were selected to have nearly the same level of physiological and pathological derangement and degree of ulcer infection.

Then a comparison was done between these three groups in terms of the following parameters: (i) duration needed to achieve complete ulcer healing. Duration of more than 10-14 days was regarded as long duration (ii) recurrence of ulcer. In other words, if venous leg ulcer infection re-occur within less than 6 months after initial discharge with complete healing, this can be considered as a bad treatment strategy (iii) development of bacterial resistance during the course of therapy or later on. And this should be confirmed by C/S test (IV) increase in wound (ulcer) size and or local spread of infection to form cellulites or abscess. During admission wound or ulcer must be checked frequently to see if there is increase or decrease of its size during the course of treatment. In addition, the development of complications such as cellulites and or abscess must be noticed (v) systemic spread of infection: septicemia. This should be confirmed by clinical picture and blood culture. (VI) the need for surgical intervention: abscess drainage, graft, flap, wound excision, leg amputation, etc (vii) Length of Hospital Stay (LOS). Hospital admission of 10-14 day was regarded as normal (viii) Cost: a cost of 20 dollar per day and 250 dollar per 10-14 day of admission was regarded as ordinary by the study (ix) patient satisfaction and quality of life during the period of treatment in terms of decreased pain, reduced odor, reduced exudates and other prodormal symptoms (x) drug side effects during or after the course of therapy such as allergic reaction or skin rash or renal toxicity or interaction with other drugs or any other significant side effect.

Data was collected on Microsoft® Excel version 16. Statistical analysis was done using the chi-squared test to compare the SLABG, SABG and LABG patients using statistical software package SPSS version 26 and relative risk was calculated using the software package MEDCALC.

Results

456 participants treated between 2015-2018 were enrolled in the study. Their ages ranged from 35 to 89 year. 58% (262/456) of these patients were female. 330 (72%) were overweight, 61 (13%) were obese and the others had normal BMI. 56% (254/456) patients had left sided venous leg ulcer. 195 (43%) patients had their infection caused by Staphylococcus *aureus* for which systemic flucloxacillin and local fucidic acid were used. 145 (32%) patients had got ulcer infected with *Pseudomonas aeruginosa* for which systemic ceftriaxone and local gentamicin were used.And the others 25% infected by *streptococcus pyogens* for which systemic penicillin and local erythromycin were used.309 (68%) had co-morbidities such as hypertension (HTN),

ischemic heart diseases (IHD) , cerbro-vascular accidents (CVA), transient ischemic attack (TIA), peripheral vascular diseases (PVD) or others. 94% (429/456) live with their families, while the rest 6% live in residential home and none of them lives alone. 72% (330/456) was smoker and 4% (18/456) was alcohol consumers. See table 1 below.

Table 1: Participants profile

Patient Characteristics	Total (n=456)	SLABG (n=151)	SABG (n=153)	LABG (n=152)	P-value
	Number (%)	Number (%)	Number (%)	Number (%)	
Age in years: mean (SD)	59.14 (16.5)	56.48 (16.8)	63.43 (15.3)	57.45 (16.6)	<.001
Gender					.99
Male	194 (42.5)	64 (42.4)	65 (42.5)	65 (42.8)	
Female	262 (57.5)	87 (57.6)	88 (57.5)	87 (57.2)	
BMI					1.0
Normal	65 (14.3)	21 (13.9)	22 (14.4)	22 (14.5)	
Overweight	330 (72.4)	110 (72.8)	110 (71.9)	110 (72.4)	
Obese	61 (13.4)	20 (13.2)	21 (13.7)	20 (13.2)	
Side of venor ulcer					.99
Left	254 (55.7)	84 (55.6)	85 (55.6)	85 (55.9)	
Right	202 (44.3)	67 (44.4)	68 (44.4)	67 (44.1)	
Type of pathogen					1.0
Staphylococcus *aureus*	195 (42.8)	65 (43.0)	65 (42.5)	65 (42.8)	
Pseudomonas aeruginosa	145 (31.8)	48 (31.8)	49 (32.0)	48 (31.6)	
Streptococus Pyogense	116 (25.4)	38 (25.2)	39 (25.5)	39 (25.7)	
Antibiotics					1.0
F&F	195 (42.8)	Both 65 (43.0)	Flu-clox 65 (42.5)	fucidic acid 65 (42.8)	
C&G	145 (31.8)	Both 48 (31.8)	ceftriaxone 49 (32.0)	Gentamicin 48 (31.6)	
P&E	116 (25.4	Both 38 (25.2)	Penicillin 39 (25.5)	erythromycin 39 (25.7)	
Co-morbidities					1.0
IHD	72 (15.8)	24 (15.9)	24 (15.7)	24 (15.8)	
CVA	63 (13.8)	21 (13.9)	21 (13.7)	21 (13.8)	
TIA	66 (14.5)	22 (14.6)	22 (14.4)	22 (14.5)	
PVD	39 (08.6)	12 (07.9)	14 (09.2)	13 (08.6)	
HTN	69 (15.1)	23 (15.2)	23 (15.0)	23 (15.1)	

No co-morbidities	147 (32.2)	49 (32.5)	49 (32.0)	49 (32.2)	
Living status					.56
With family	429 (94.1)	140 (92.7)	146 (95.4)	143 (94.1)	
In residential home	27 (5.9)	11 (7.3)	7 (4.6)	9 (5.9)	
Smoking					.98
Smokers	330 (72.4)	110 (72.8)	110 (71.9)	110 (72.4)	
Non-smokers	126 (27.6)	41 (27.2)	43 (28.1)	42 (27.6)	
Alcohol consumption					1.0
Drinkers	18 (3.9)	6 (4.0)	6 (3.9)	6 (3.9)	
Non-Drinkers	438 (96.1)	145 (96.0)	147 (96.1)	146 (96.1)	

Chi-squared test or ANOVA (as appropriate) was used to compare the SLABG, SABG and LABG patients.

Comparison of treatment strategies SABG, LABG and SLABG in terms of (i) the duration needed to achieve ulcer healing (ii) ulcer recurrence:

Table 2 shows that most patients 71% (107/151) who had received both systemic and local antimicrobial therapy (SLABG) had achieved complete ulcer healing and infection control within the standard period (10-14 day). On the other hand, only around 30% of the patients (48/153) who received systemic antibiotics only (SABG) and those who had local antibiotics only (LABG: 45/152) got ulcer healed within 10-14 days. Ulcer healing within the usual duration of 10-14 days was 2.4 time higher (relative risk 2.4, 95% CI: 1.84, 3.12) under the combination modality (SLABG) compared to other single treatment strategies.

Similarly, the study revealed that most of patients (72%) who were treated by a combination modality (SLABG) had not got ulcer recurrence within six months after initial discharge (109 out of 151). On the other hand, fewer patients (around 30%) in the other groups (44/153 in SABG and 42/152 in LABG) did not get recurrences of the ulcer within 6 months after initial healing, see table 2. The chi-squared test confirmed that the significant association between treatment strategies and recurrence rate of ulcer ($P<.001$). The probability of not recurring ulcer was 2.6 time higher (relative risk 2.6, 95% CI: 1.98, 3.44) under the combination modality (SLABG) compared to other single treatment strategies. See table 2 below:

Table 2: Duration needed to achieve ulcer healing, ulcer recurrence, development of bacterial resistance, increase in wound size and or abscess or cellulites during therapy, and development of septicemia and the need for surgical intervention according to treatment strategies

Parameters	SLABG: 151 No. (%)	SABG: 153 No. (%)	LABG: 152 No. (%)	P-value	$RR_{(SL\ vs\ L)}$ (95% CI)

Duration of ulcer healing				<.001	
Within 10-14 day	107 (71)	48 (31)	45 (30)		2.4
More than 14 day	44 (29)	105 (69)	107 (70)		(1.84, 3.12)
Ulcer recurrence within 6 months				<.001	
No	109 (72)	44 (29)	42 (28)		2.6
yes	42 (28)	109 (71)	110 (72)		(1.98, 3.44)
Bacterial resistance				<.001	
No	104 (69)	112 (73)	145 (95)		0.72
yes	47 (31)	41 (27)	7 (5)		(0.65, 0.81)
Abscess or cellulites				<.001	
No	127 (84)	25 (16)	24 (16)		5.3
yes	24 (16)	128 (84)	128 (84)		(3.66, 7.74)
Septicemia				<.001	
No	142 (94)	114 (75)	98 (65)		1.4
Yes	9 (6)	39 (25)	54 (35)		(1.27, 1.64)
Surgical intervention				<.001	
No	138 (91)	110 (72)	106 (70)		1.3
Yes	13 (9)	43 (28)	46 (30)		(1.17, 1.47)

P-value is calculated based on Chi-squared test to compare the SLABG, SABG and LABG patients. SL: SLABG, L: LABG. RR: Relative Risk, Bold indicates the outcome category for the RR.

Comparison of treatment strategies in terms of (iii) development of bacterial resistance (IV) increase in wound (ulcer) size and or local spread of infection to form cellulites or abscess:

It had been found, see table 2, that 31% of the patients (47/151) who had received both systemic and local antimicrobial therapy (SLABG) had developed bacterial resistance. Nearly a similar number of the patients 27% (41/153) who received systemic antibiotics only (SABG) had got the same problem (emergence of antibiotics-resistant micro-organism). Meanwhile, only 5% patients who had local antibiotics and or antiseptics (LABG: 7/152) had got bacterial resistance. Therefore, the probability of no bacterial resistance was 28% lower (relative risk 0.72, 95% CI: 0.65, 0.81) under the combination modality (SLABG) compared to local treatment strategy (LABG). Treatment strategy SABG also had the similar lower probability.

On the contrary, most of patients (127/151=84%) who were treated by a combination modality (SLABG) had not got increased wound size or abscess or cellulites during therapy. On the other hand, only very few patients (16%) in the other groups (25/153 in SABG and 24/152 in LABG) had not got increased wound size or abscess or cellulites during therapy. Chi-squared test confirmed the significant

association between treatment strategies and wound size (*P*<.001). The probability of not getting increased wound size or abscess or cellulites during therapy was more than 5 time higher under combination therapy (SLABG) compared to single treatment strategies (relative risk 5.3, 95% CI: 3.66, 7.74).

Comparison of treatment strategies in terms of (v) systemic spread of infection: septicemia (VI) the need for surgical intervention: abscess drainage, graft, flap, wound excision, leg amputation, etc:

The study revealed that very few patients (9 out of 151: 6%) in the SLABG group (the patients who had received both systemic and local antimicrobial therapy) had developed septicemia. Whereas, this percentage was much higher (at least 25%) in the other groups. 25% (39/153) who received systemic antibiotics only (SABG), and 35% (55/152) who had local antibiotics only (LABG). Similarly, only 9% of patients who were treated by a combination modality (SLABG 13/151) had required surgical intervention in the form of abscess drainage or skin graft or flap while around 30% patients in the other groups (43/153 in SABG and 46/152 in LABG) needed surgical intervention in the form of abscess drainage or skin graft or flap See table 2 for details. The probability of not developing septicemia was 40% higher under combination therapy (SLABG) compared to single treatment strategy of LABG (relative risk 1.4, 95% CI: 1.27, 1.64). Similarly, the probability of not requiring surgical intervention was 30% higher under combination therapy (SLABG) compared to single treatment strategy of LABG (relative risk 1.3, 95% CI: 1.17, 1.47).

Economic evaluation: Comparison of treatment strategies in terms of (vii) length of hospital stay (LOS) and (viii) Cost:

Table 3 presents the comparative results for length of hospital stay and related costs and patient satisfaction. It had been found that 87% (133/153) patients, who were treated by systemic antibiotics only (SABG), and 89% (135/152) patients, who received local antibiotics and or antiseptics only (LABG), had prolong hospital stay (more than 14 day) with subsequent more cost (more than 250 dollar). Meanwhile, only 12% patients (18/151) who had treated by the combination of both systemic and local antimicrobial agents (SLABG) had prolong admission and more cost. This advantage of fewer patients needed prolonged hospital stay and hence lower cost of treatment under SLABG treatment strategy over the other two strategies was statistically significant (P<.001) and 8 times more likely (relative risk 7.9, 95% CI: 5.01, 12.37).

Table 3: Length of hospital stay (LOS), Cost and patient satisfaction according to treatment strategy

Parameters	SLABG: 151	SABG: 153	LABG: 152	P-	RR ($_{SL\ vs\ L}$)

	No (%)	No. (%)	No. (%)	value	(95% CI)
Length of stay				<.001	
Usual: 10-14 days	133 (88)	20 (13)	17 (11)		7.9
Prolong: > 14 days	18 (12)	133 (87)	135 (89)		(5.01, 12.37)
Cost				<.001	
Usual: 250 dollar	133 (88)	20 (13)	17 (11)		7.9
Costly: >250 dollar	18 (12)	133 (87)	135 (89)		(5.01, 12.37)
Patient satisfaction				<.001	
Satisfied	125 (83)	47 (31)	39 (26)		3.2
Not satisfied	26 (17)	106 (69)	113 (74)		(2.44, 4.27)

P-value is calculated based on Chi-squared test to compare the SLABG, SABG and LABG patients. SL: SLABG, L: LABG. RR: Relative Risk, Bold indicates the outcome category for the RR.

Comparison of treatment strategies in terms of (ix) patient satisfaction and quality of life during the period of treatment: pain and other prodormal symptoms (x) drug side effects:

Table 3 shows that 83% (125/151) of the patients who had received combination treatment (SLABG) were satisfied during the course of treatment in terms of decreased pain, reduced odor, reduced exudates and other prodormal or constitutional symptoms. On the other hand, most of the patients, around 70% of patients who did not have combination treatment (106/153 in SABG and 113/152 in LABG) were not satisfied during the therapy. They were upset, unwell and with pain and other prodormal symptoms. The patients who had received combination treatment (SLABG) were at least 3 times more satisfied during the course of treatment compared to single treatment strategies (relative risk 3.2, 95% CI: 2.44, 4.27).

Regarding the development of drug side effects: apart from emergence of resistant micro-organism, none of the patients in all three groups had got significant side effects

Discussion and Conclusion

Venous leg ulcer is defined as chronic and complicated wound that usually affects medial side of the leg. The real underlying pathology is not well known. However, there are some mechanisms which might explain such ulcer. It is thought that this venous ulceration might arise due to incompetent venous valvular system. This in turn can lead to venous stagnation and then extravasations of blood and mediators of inflammation underneath the skin with subsequent tissue breakdown and ulcer formation. 17

In addition, this venous ulcer almost always can get infected with multiple pathogens. And this infection can further delay ulcer healing and can cause many problems to the patients. Therefore, the key point is to control such infection in order to ensure safe healing of the venous ulcer. 18

To deal with venous ulcer, two important points should be taken into consideration. First point is the management of incompetent valves and other dilated veins or varicosities. The second point is infection control which is the most important and vital step in the whole process.18,19 Many ways are usually followed to treat venous leg ulcer infection such as systemic antibiotics or local antibiotics or local antiseptics or a combination of systemic and local routes. For each option there are some advantages and drawbacks. This current study aimed to shine the light and to find out which option is the best in terms of achievement of safe ulcer healing and patient satisfaction. The significance of this current study is great because it can improve health practice with subsequent achievement of patient safety. 19, 20

This current study revealed that best results can be achieved by combination of systemic antibiotics and local antibiotics. It had been found most of the participants, who had both systemic and local antimicrobials showed these results: (i) they had achieved infection control and ulcer healing within reasonable duration(10-14 days) (ii) they had not got recurrence of ulcer within 6 months after initial healing (iii) they had not got complications such as cellulitis or abscess or septicemia during or after the course of therapy (iv) they did not required surgical intervention in the form of abscess drainage or skin graft or flap or leg amputation during treatment period (v) they had not stayed in the hospital for prolong period of admission and without extra cost (vi) they were satisfied in terms of decreased pain, reduced odor, reduced exudates and other prodormal or constitutional symptoms and (vii)they had not got significant drug side effects.

On the other hands, most of participants who had either systemic antibiotics only or local antibiotics only showed the following results: (i) they had not achieved infection control and ulcer healing within reasonable duration(10-14 days) and they needed prolong duration to achieve wound healing. (ii) they had got recurrence of ulcer within 6 months after initial healing (iii) they had got complications such as cellulitis or abscess or increased wound size or septicemia during or after the course of therapy (iv) they required surgical intervention in the form of abscess drainage or skin graft or flap during treatment period (v) they had stayed in the hospital for prolong period of admission and with extra cost (vi) they were not satisfied in terms of decreased pain, reduced odor, reduced exudates and other prodormal or constitutional symptoms.

Only a single drawback had been noticed with the use of systemic antibiotics. This is the emergence of antibiotics-resistant micro-organism. However, the advantages and patient satisfaction that could be achieved from systemic antibiotics can out-weight this single side effect.

Although there are similar studies in the same field, this current study is unique. Most of other studies compared between systemic antibiotics alone in one hand and between the use of local route alone in the other hand.[21] Meanwhile, our study compared the combination of both routes in addition to the use of each route alone. Therefore, it is regarded as a new trial in the field of antimicrobial therapy for venous leg ulcer infection.

Meara et al which reviewed forty-five RCTs reporting 53 comparisons and recruiting a total of 4486 participants concluded that: at present, no evidence is available to support the routine use of systemic antibiotics in promoting healing of venous leg ulcers. However, the lack of reliable evidence means that it is not possible to recommend the discontinuation of any of the agents reviewed. [21]

In terms of topical preparations, some evidence supports the use of cadexomer iodine. Current evidence does not support the routine use of honey- or silver-based products. Further good quality research is required before definitive conclusions can be drawn about the effectiveness of povidone-iodine, peroxide-based preparations, ethacridine lactate, chloramphenicol, framycetin, mupirocin, ethacridine or chlorhexidine in healing venous leg ulceration. In light of the increasing problem of bacterial resistance to antibiotics, current prescribing guidelines recommend that antibacterial preparations should be used only in cases of clinical infection, not for bacterial colonization. [21]

As with other studies, this current research had some limitations. The retrospective mode of study can miss pitfalls related to the course of therapy, progression, prognosis and complications. Therefore, clinical trial with prospective stronger evidence is recommended for future studies. Although the sample size of this study was not calculated prospectively, the study had enough power as all the considered parameters were statistically significant. Moreover, this study was performed in a single center only and therefore a multi-center future study is highly recommended

Ultimately, our current study concluded that the combination of systemic antibiotics together with local antibiotics or antiseptics could achieve good results in terms of venous ulcer healing and infection control with reasonable duration, less complications, less recurrence rate and a good degree of patient satisfaction.

However, both groups SLABG and SABG had developed significantly higher bacterial resistance than the LABG group

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